04-18-05

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APR 13 2005

IN THE U.S. PATENT AND TRADEMARK OFFICE

Inventor	Gabor BOGYE	
Patent App.	09/890,029	
Filed	24 July 2001	Conf. No. 6045
For	PHARMACEUTICAL COMBINATION OF PROGESTERONE AND FOLIC ACID	
Art Unit	1617	Examiner Hui, S

Hon. Commissioner of Patents
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Alexandria, VA 22313-1451

SECOND AMENDMENT - AFTER FINAL ACTION

This is in response to the Office Action mailed 27 January 2005.

REMARKS

This response is submitted under 37 CFR 1.116 after final rejection because Applicant believes that all claims are in condition for allowance. In any event entry of this response will place the application in better form for appeal. No new matter has been added and no new issues have been raised. Finally the points raised herein are in direct response to points raised by the Examiner in the last office action and Applicant could not have made his response at an earlier date.

The Examiner has finally rejected all of the claims in the application. All of the claims have been rejected as anticipated under 35 USC 102. Claims 9 through 13, 15, 16, 21 and 22 have been rejected as anticipated in view of newly cited ALI et al in combination with the USDA Nutrient Database, Release 12, 1998 (Monograph No. 01077. Claims 19, 20, 23, 24 and 25 have been rejected in view of either the SPELLACY et al or BUTTERWORTH et al references as applied in the previous office action. Furthermore claims 9, 13 through 15, and 17 and 18 are rejected under 35 USC 112, first paragraph, as beyond the scope of the enabling disclosure. The Examiner still believes that the only compounds that are enabled by the specification to function as a plasma homocysteine reducing agent are the specific compounds set forth in claim 10, all of which are established co-vitamins that have been used to treat patients with hyperhomocysteinaemia. The Examiner refuses to accept Applicant's functional definition of these compounds, not because he does not believe that the screening methods disclosed in the references are not effective to determine if a particular compound does in fact have the ability to reduce plasma homocysteine levels. The Examiner does not believe that Applicant or anyone else skilled in the art knows of any additional compounds besides those of claim 10 that would likely possess plasma homocysteine reducing activity. The Examiner argues that

the screening tests disclosed in the Abbott Laboratories reference cited by the Applicant are of no help to establish the sufficiency of the disclosure provided by the specification for the term plasma homocysteine reducing agent when the specification provides no guidance as to what compounds besides those of claim 10 would be expected to function as plasma homocysteine reducing agents. The Examiner further argues that the compounds functioning as the plasma homocysteine reducing agents are the point of novelty with respect to the present invention and that decisions by the U.S. Courts rule that it is improper to define an ingredient functionally when such an ingredient is the point of novelty of the invention.

Applicant disagrees. The point of novelty in the present invention is not the plasma homocysteine reducing agents. Applicant does not contend that he has discovered any novel plasma homocysteine reducing agents. What Applicant has discovered is the administration of a plasma homocysteine reducing agent to a patient undergoing treatment with a gestagen hormone for the treatment of a variety of illnesses to reduce a risk to the patient of thromboembolism. The risk of thromboembolism is reduced because the patient's plasma homocysteine level is lowered. No one else has ever administered to a patient undergoing therapy with a

gestagen hormone, a compound for the stated purpose of reducing plasma homocysteine levels. The plasma homocysteine agent may be one of the specified vitamin co-factors disclosed on page 4 of the application or it may be penicillamine or a nucleoside analogue as disclosed in the prior art previously made of record by the Applicant. It is also possible that in the future other researchers will find new plasma homocysteine reducing agents. Any potential new plasma homocysteine reducing agents may be tested according to the Abbott Laboratories protocol and if successful should also fall within the scope of the presently claimed invention. The fact that Applicant has not himself discovered any new plasma homocysteine reducing agent does not mean that he must be limited only to those plasma homocysteine reducing agents known in the art.

It is perfectly proper to define an ingredient in functional terms, rather than in purely structural terms and such a definition of an ingredient is not beyond the scope of the enabling disclosure provided by the specification when the Applicant has given several representative examples in his application of compounds that are plasma homocysteine reducing agents, has provided collateral art to show additional compounds that are effective plasma homocysteine reducing agents, and has provided a

test to screen other compounds that are potential plasma homocysteine agents. The decisions cited by the Examiner do not relate to such a fact situation. One of the decisions relates to a biotechnology patent application where the ingredient defined in functional terms encompassed novel nucleic acid molecules, none of which had actually been made, let alone tested.

Applicant has amended claims 9 and 15 to recite that the gestagen hormones are administered to patients for specific utilities other than for female contraception. Female contraception is the utility for the gestagen hormones administered according to SPELLACY et al and BUTTERWORTH et al. As a result the Examiner has not applied these two references against claims 9 and 15 and the claims dependent upon either of these two independent claims. Instead the Examiner has found and applied the ALI et al reference which he contends anticipates claims 9 and 15 and the claims dependent thereon. The ALI reference discloses the administration of a gestagen hormone to older female patients for the purpose of hormone replacement therapy. The ALI et al reference does not specifically disclose administering to the patients a plasma homocysteine reducing agent together with the gestagen hormone. However, ALI et al encourages the patient undergoing hormone replacement therapy to consume milk and milk

products as well as other sources of calcium. The Examiner then has found the USDA Nutrient Database, Release 12 which discloses that milk contains a number of B Vitamins, including folic acid, Vitamin B_6, and Vitamin B_{12}. The Examiner concludes that such a patient described in ALI et al is inherently undergoing the same therapy as is covered in claims 9 and 15 of the present application and therefore ALI et al is anticipatory of these claims and the claims depending on these claims.

Applicant does not agree. It is clear in ALI et al that the patients undergoing hormone replacement therapy with a gestagen hormone are post-menopausal women at risk for osteoporosis. Accordingly ALI et al is concerned that the patients will have sufficient calcium intake so that osteoporosis can be minimized. Providing calcium intake is the sole reason mentioned in ALI et al for the patients to consume milk and milk products such as yogurt. Even though there is some B Vitamin content in milk, there is not the slightest suggestion in ALI et al that the B Vitamins are a factor at all in the treatment of these patients. Therefore there is certainly no express disclosure or even a suggestion of the invention as covered in claims 9 and 15 and the claims dependent thereon in ALI et al.

Furthermore there is no inherent disclosure of the invention in present claims 9 and 15 in ALI et al. The USDA Nutrient Database, Release 12 indicates that a 100 g serving of milk (about 3.5 ounces of milk) contains 0.042 mg of Vitamin B_6, 5μg of folic acid and 0.36μg of Vitamin B_{12}. All three of these concentrations of B Vitamins are much lower than the therapeutically effective amount of the B Vitamins as defined in the specification on page 6, lines 25 to 30. Therefore there is no inherent disclosure of the present invention in ALI et al. In order to consume enough milk to obtain 0.5 mg of folic acid in a day (the minimum therapeutically effective daily dosage), the patient would have to consume 100 times the amount of milk shown in the USDA Nutrient Database, Release 12, that is about 350 ounces of milk or about 10 liters of milk a day. For Vitamin B_6 in order to obtain the minimum therapeutically effective daily dosage of 10 mg, the patients would have to consume about 830 ounces of milk a day well above 10 liters. For Vitamin B_{12} in order to obtain the minimum therapeutically effective daily dosage of 300 μg, the patients would have to consume about 2900 ounces of milk a day which is almost 100 liters. These amounts of milk are not realistic figures and so it is not seen how ALI et al either inherently anticipates or renders obvious the invention in claims 9 and 15.

Applicant has not been able to convince the Examiner that the BUTTERWORTH et al and SPELLACY et al references do not inherently anticipate claims 19, 20, 23, 24 and 25 even though independent claims 19 and 20 define the patient as "an otherwise healthy patient taking a gestagen hormone composition for contraception to reduce a risk to the patient of thromboembolism induced by taking the gestagen hormone." SPELLACY et al discloses administration of 30 mg of Vitamin B_6 (see page 267, near the bottom) together with a gestagen hormone for female contraception to correct the adverse effects of the gestagen hormone on carbohydrate metabolism. This is a different utility from that of the presently claimed method where plasma homocysteine levels are lowered by catalytic metabolism of the homocysteine using Vitamin B_6 as a co-factor. The Examiner argues, however, that all patients undergoing gestagen hormone therapy have elevated plasma homocysteine levels even though the prior art does not expressly say so and so when the SPELLACY et al patients undergo gestagen hormone therapy, they have elevated homocysteine levels and when those same patients also take the Vitamin B_6, those plasma homocysteine levels must drop. See page 8, central paragraph of the office action.

The patients treated according to the method of claims 19, 20, 23, 24 and 25 are characterized as "otherwise healthy patients" which means that the patients do not suffer from the side effect of carbohydrate metabolism disruption. Thus the SPELLACY et al reference does not inherently discloses the presently claimed invention.

In BUTTERWORTH et al the situation is similar. Female patients receiving a gestagen hormone for contraception are also administered folic acid in a dosage of 10 mg/day. The patients are receiving the folic acid not for reducing an elevated plasma homocysteine level, but are receiving the folic acid to treat dysplasia of the uterine cervix. This cytological effect sometimes results when women take gestagen hormones for contraception. In claims 19, 20, 23, 24 and 25 the patients are characterized as "otherwise healthy patients" meaning that these patients do not have dysplasia of the uterine cervix. Thus BUTTERWORTH et al does not inherently discloses the presently claimed invention.

Applicant now has the following direct comments regarding the present application and the patentability of the claims in this application over the cited prior art:

As for the publication ALI et al cited by the Examiner in the final rejection, it seems that the text of the full publication was not considered by the Examiner, as only the abstract was enclosed with the office action. Applicant has obtained a copy of the full publication which is enclosed herewith. On page 532, column 2, lines 1 through 3, the following is written:"Although hormone users reported higher calcium intake and greater exercise participation than nonusers, the difference was not significant." This sentence provides further evidence that women taking HRT did not take therapeutically effective amounts of plasma homocysteine content reducing agents occurring in milk (e.g. folic acid). The abstract includes only the first part of the above cited sentence and the important end of the sentence, i.e. "the difference was not significant" is missing from the abstract.

Applicant specifically tested his contraception patients for carbohydrate metabolism problems and none of the patients had this problem. Thus all of Applicant's conception patients were otherwise healthy. The SPELLACY et al reference discloses contraception patients who have developed carbohydrate metabolism disorders while undergoing the contraception. Thus the SPELLACY et al patients are different patients from the patients treated according to the presently claimed invention, including the

patients receiving contraception. Please also note that taking gestagen hormones as a contraceptive is relatively contraindicated for patients having carbohydrate metabolism problems.

At the end of the office action the Examiner has alleged that all patients taking progesterone (a gestagen hormone) have elevated homocysteine levels in the blood because homocysteine-elevating activity of progesterone is inherently present in patients taking this drug. Applicant cannot confirm that all patients taking a gestagen hormone for contraception or for any other medicinal purpose have elevated plasma homocysteine levels. All of Applicant's patients were healthy patients, they had neither carbohydrate metabolism problems not Vitamin B_6 depletion problems.

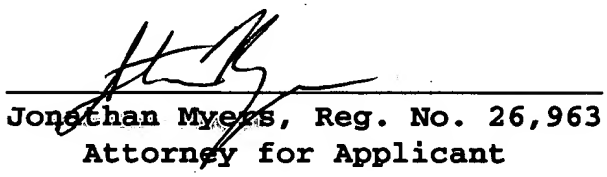
The Examiner notes that the prior art that he has cited is silent with regard to the patient's plasma homocysteine levels. According to the BRATTSTROM et al reference cited and discussed in the background portion of the present application on page 3 and made of record on 2 January 2002 in an Information Disclosure Statement not all patients taking a gestagen contraceptive have elevated plasma homocysteine levels though there is evidence that all of these patients do suffer from a depletion of the B Vitamin co-factors. No connection is disclosed in BRATTSTROM et al between gestagen hormone administration and elevated plasma levels of

homocysteine. Accordingly the correlation between the administration of a gestagen hormone to patients and elevated plasma homocysteine levels in the patient was found by the present Applicant. Thus there is no general recognition in the prior art that there is a direct correlation between administration of a gestagen hormone to a patient and an increase in the plasma concentration of homocysteine in that patient.

Finally Applicant wishes to make of record a copy of the Second Examination Report issued on 16 February 2005 by the European Patent Office in the corresponding European Patent Application. No new document has been cited in the Second Examination Report and the First Examination Report and all cited references are of record in the present application. Applicant nots that the European Patent Office considered the invention as free of the prior art since there is no disclosure or suggestion in the prior art that refers to elevated plasma homocysteine levels or the prevention of thromboembolic side effects in persons taking gestagen type hormones.

Applicant believes that all claims now presented are allowable and a response to that effect is earnestly solicited.

Respectfully submitted,
The Firm of Karl F. Ross P.C.



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Enclosures: Second European Patent Office Examination Report
ALI et al Reference

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Application No.	Ref.	Date
00 903 916.5 - 2107	0546-56984EP/SF	16.02.2005
Applicant: Bogye, Gabor		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).

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Blott, C
Primary Examiner
for the Examining Division

Enclosure(s): 5 page/s reasons (Form 2906)

Registered Letter
EPO Form 2001 07.02CSX

The examination is being carried out on the **following application documents:**

Description, Pages

1-11 received on 19.07.2004 with letter of 19.07.2004

Claims, Numbers

1-6 received on 19.07.2004 with letter of 19.07.2004

1. The amendments filed with the letter dated 19.07.2004 introduce subject-matter which extends beyond the content of the application as filed, contrary to Art. 123(2) EPC. The amendments concerned are the following:
a) claim 1 and p. 4, l. 2, 16, 23: "...induced by gestagen type hormones..."
Amended claim 1 may be restricted to "... induced by gestagen type hormone containing compositions (or medicines)..." in accordance with p. 1, l. 7 and p. 4, l. 14.
b) p. 5, l. 10: "...including a progesterone type hormone..."
It seems that there is no basis for this amendment in the application as originally filed.

2. The difference between the terms "gestagen type hormone" and "progesterone type hormone" used in claims 5 and 6 and in the description is not clear to the Examining Division (Art. 84 EPC).
In this context, it is pointed out that the priority document only refers to "progesterone type hormones". Priority might therefore not be considered valid regarding "gestagen type hormones". The final assessment of novelty pursuant to Art. 54(3) and (4) EPC will therefore be done subsequently.

3. References:
D1: JOURNAL OF WOMEN'S HEALTH AND GENDER-BASED MEDICINE, 1999, 8/9, pages 1167-1172
D2: GB 2 131 292
D3: JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, vol. 2, no. 3, 1983, pages 221-230, ISSN: 0731-5724
D4: AMERICAN JOURNAL OF CLINICAL NUTRITION, vol. 35, no. 1, January 1982, pages 73-82
D5: THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, vol. 226, no. 12, 17 December 1973, pages 1421-1424, ISSN: 0098-7484
D6: JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, vol. 277, No. 22, June 1997, pages 1775-1781
D7: New England Journal of Medicine, vol. 334, March 1996, No. 12, pages 759-

762

✓ D8: AMERICAN JOURNAL OF CLINICAL NUTRITION, vol. 65, No. 2, February 1997, pages 572-573

✓ D9: WO 0038691

a) According to D1, elevated plasma homocysteine levels have been associated with increased atherosclerotic disease risk and estrogen or estrogen/progestin replacement therapy have been suggested to lower plasma homocysteine levels in postmenopausal women. In a clinical trial, plasma homocysteine levels decreased in postmenopausal women randomized to placebo, estrogen and estrogen/progestin replacement therapy (cf. Table 2). B vitamin intake did not differ among treatment groups (cf. table 3). D1 thus does not refer to elevated plasma homocysteine levels or the prevention of thromboembolic side effects in persons taking gestagen type hormones.

b) D2 refers to the treatment of hair loss in men and is thus not relevant for the assessment of novelty and inventive step.

c) D3 refers to a study wherein both folate from orange juice and synthetic folic acid increased serum folate concentration in women ingesting a folate restricted diet. Women using combination type oral contraceptives (OCA) had lower folate serum than non-users at the inception of the study. D3 thus does not refer to elevated plasma homocysteine levels or the prevention of thromboembolic side effects in persons taking gestagen type hormones.

d) D4 refers a clinical trial wherein the manifestation of dysplasia and megaloblastis in uterine cervix improved after folic acid supplementation in women using combination type OCAs (cf. abstract and page 79, left column, lines 15-20 from the bottom). OCA users had lower red cell folate values and plasma B12 levels than non-users (cf. abstract and page 78, right column, lines 14-18). D4 thus does not refer to elevated plasma homocysteine levels or the prevention of thromboembolic side effects in persons taking gestagen type hormones.

e) D5 refers to a study wherein the treatment with folic acid reverted to normal or improved megaloblastic abnormalities of cervicovaginal cells similar to those seen in severe folate and vitamin B12 deficiency, in women taking OCAs (combination type or progestogens only) (cf. abstract). In this study, 17-21% of the women had decreased serum folate concentration. D5 thus does not refer to elevated plasma homocysteine levels or the prevention of thromboembolic side effects in persons taking gestagen type hormones.

f) D6 refers to a study wherein elevated plasma homocysteine level was shown to be a risk factor for artherosclerotic vascular diseases (cf. abstract). It also increases the risk associated with smoking and hypertension (cf. abstract). Plasma homocysteine concentrations relates inversely to blood levels of folate, cobalamin and pyridoxine and to intakes of these vitamins (cf. page 1780, left column, lines 5- 14). D6 thus does not refer to elevated plasma homocysteine levels or the prevention of thromboembolic side effects in persons taking gestagen type hormones.

g) D7 refers to a study wherein it was shown that high plasma homocysteine levels are a risk factor for deep-vein thrombosis (cf. abstract). Elevated plasma homocysteine levels may result from low levels of folic acid, vitamin B6 or B12. According to the authors of D7, it remains to be tested wether homocysteine-lowering therapy with vitamins can prevent recurrent venous thrombosis (cf. page 762, left column, line 13 from the bottom, to end of document). D7 thus does not refer to elevated plasma homocysteine levels or the prevention of thromboembolic side effects in persons taking gestagen type hormones.

h) According to D8, supplements comprising folate associated with vitamin B12 may be used for the prevention of vasculotoxic hyperhomocysteinemia and thereby the prevention of thrombotic strokes and peripheral venous thromboses (cf. page 572, right column, lines 22-29). D8 thus does not refer to elevated plasma homocysteine levels or the prevention of thromboembolic side effects in persons taking gestagen type hormones.

i) D9 discloses combinations of estrogen and progestogen for oral contraception, which may comprise nutritional supplements such as folic acid (cf. p. 5, l. 6, claims 1-27). D9 thus does not refer to elevated plasma homocysteine levels or the prevention of thromboembolic side effects in persons taking gestagen type hormones.

4. None of the cited documents discloses or anticipates the use of a plasma homocysteine content reducing agent for the reduction of thromboembolic side effect risk induced by gestagen type hormone containing medicines. The subject-matter of claims 1-6 consequently might be considered new (Art. 54 (1)-(5) EPC).

5. The subject-matter of claims 1-6 involves an inventive step in the sense of Art. 56 EPC for the following reasons.

a) Document D5 might be considered the most relevant state of the art.
As mentioned above, D5 refers to a study wherein the treatment with folic acid reverted to normal or improved megaloblastic abnormalities of cervicovaginal cells

similar to those seen in severe folate and vitamin B12 deficiency, in 115 healthy women taking OCAs (combination type or progestogens only). In this study, 17-21% of the women had decreased serum folate concentration.

The problem to be solved by the present invention in view of D5 can be regarded as the reduction of thromboembolic side effects induced by gestogen hormones.

The solution of said problem according to the present application is the use of a plasma homocysteine content reducing agent.

It is already known from D6-8 that low levels of folic acid, vitamin B6 or B12 ...induce elevated plasma homocysteine levels, which are a risk factor for thromboembolic diseases, which might be prevented by homocysteine-lowering therapy.

In the study of D5, only 17-21% of the women taking OCAs (combination type or progestogens only) had decreased serum folate concentration.
It is therefore not possible, on the basis of D5 in combination with D6-8, to conclude that gestogen type hormone systematically lead to (subnormal levels of vitamins and consequently) elevated plasma homocysteine levels, which are responsible for an increased risk for thromboses. Furthermore, the Applicant confirmed with telefax of 06/03/01, that most patients did not have decreased serum folate concentrations or that there was no relationship between the elevated plasma homocysteine levels and the serum folate concentrations in the examples of the present application.
There is thus no incentive for the skilled person to combine the teaching of the aforementioned documents and the use of a plasma homocysteine content reducing agent for the reduction of thromboembolic side effect risk induced by a gestagen type hormone containing medicines consequently is not rendered obvious by the cited prior art documents.

b) Alternatively, documents D6-8 might be considered the most relevant state of the art.
It is already known from D6-8 that low levels of folic acid, vitamin B6 or B12 ...induce elevated plasma homocysteine levels, which are a risk factor for thromboembolic diseases, which might be prevented by homocysteine-lowering therapy.

The problem to be solved by the present invention in view of D6-8 can be regarded as the prevention of thromboembolic side effects induced by gestogen hormones.

The solution of said problem according to the present application is the use of a plasma homocysteine content reducing agent.

For the man skilled in the art, this solution is not rendered obvious by D6-8 taken alone or in combination with any of the cited documents. Indeed, the thromboembolic diseases enumerated in D6-8 are all clearly linked to a problem of plasma hyperhomocysteinemia.
It is not disclosed or suggested by any of the cited documents that gestagen medicines lead to plasma hyperhomocysteinemia (cf. above). Furthermore, persons taking hormones were excluded from the tests done in D7, to clearly identify plasma hyperhomocysteinemia as a separate risk factor. When starting from D6-8, there is thus no motivation for the skilled person to use a plasma homocysteine reducing agent for the reduction of the thromboembolic side effect risk of gestagen containing medicines.

c) The Applicant has provided evidence for the claimed effect on p. 8-11 of the description and in his letter dated 06.03.2001.

6. The attention of the Applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Art. 123 EPC).
When amending claims, the Applicant is requested to identify those passages in the application as originally filed on which the amended claims are based (Guidelines E-II, 1.).